

**REMARKS**

Claims 33-36, 39-44, 47-52, and 55-59 were pending. Claims 33, 41, 50, and 59 have been amended and claims 42-43, 47 and 57-58 have been canceled without prejudice.

Claim 41 has been amended to specify a full complement of CDRs.

Claims 33, 50 and 59 have been amended to specify that the recited compositions do not include an adjuvant or immunostimulatory agent. Support for this amendment can be found throughout the specification and claims as originally filed, *e.g.*, page 25 (lines 13-16) and page 34 (lines 24-27).

The foregoing claim amendments should in no way be construed as acquiescence to any of the Examiner's rejections and were made solely to expedite prosecution of the application. Applicants reserve the right to pursue claims to the canceled subject matter, or any subject matter which they are entitled to claim, in this or a separate application. No new matter has been added.

***Rejection of Claims 33-36, 39-44, 47-52, and 55-59 Under 35 U.S.C. §103(a)***

Claims 33-36, 39-44, 47-52, and 55-59 are rejected as being unpatentable over WO 01/85798 in view of US 5,869,057. The Examiner acknowledges that WO 01/85798 "does not teach the use of  $\beta$ hCG as an antigen." However, the Examiner relies on US 5,869,057 as teaching "the use of  $\beta$ hCG as an antigen", as well as its use in "immunization against  $\beta$ hCG and an antimetastasis treatment." The Examiner further asserts that Applicants' previous arguments that the  $\beta$ hCG-based vaccine described in the '057 patent would not have motivated one of ordinary skill in the art to link  $\beta$ hCG with an antibody, since the '057 patent requires the presence of an adjuvant, are unpersuasive because "Applicant[s are] arguing limitations not claimed."

Applicants respectfully traverse this rejection for previously made of record. However, to expedite prosecution and allowance of the pending claims, claims 33, 50 and 59 have been amended to specify that the recited compositions do not contain *an adjuvant or immunostimulatory agent*. As explained in Applicants' previous response of September 3, 2008, the '057 patent fails to teach or suggest combining  $\beta$ hCG with an antibody to form a molecular conjugate which directly targets the human MMR on APCs without an adjuvant or immunostimulatory agent, as claimed. Nor would there have been motivation to have made such a molecular conjugate based on what was known in the art concerning  $\beta$ hCG.

The '057 patent teaches the use of the antigen,  $\beta$  human chorionic gonadotropin ( $\beta$ hCG), for use as a vaccine. Specifically, the '057 patent teaches linking a microbial (non-self) gene product (e.g., a prokaryotic helper T cell epitope, such as heat-labile enterotoxin B subunit (LTB)) to a *"self" gene product* (e.g., a  $\beta$ hCG epitope) for the production of an immune response to the self protein. According to the '057 patent, the use of "foreign (non-self) T cell epitopes and the natural adjuvant properties of microbial gene products" is required to produce a therapeutically acceptable vaccine (see, e.g., col. 11, lines 19-23). Such adjuvants *"must be included in the vaccine formulation in order for processing and presentation of T cell epitopes by specialized antigen presenting cells such as macrophages and dendritic epidermal cells to occur"* (col. 11; lines 3-7) (emphasis added). Therefore, based on the teachings of the '057 patent, one of ordinary skill would not have been motivated to have linked  $\beta$ hCG with an antibody to generate an immune response, as claimed, since it was well known that antibodies are not microbial gene products, and do not have microbial adjuvant properties, such as helper T cell epitopes.

Moreover, at the time the present application was filed, human  $\beta$ hCG antigen was well known to be "self-tolerant." Accordingly, to break this tolerance, it was understood by those skilled in the art that a  $\beta$ hCG-based vaccine *must* include a potent carrier, as well as combining it with an adjuvant. See, for example, the '057 patent, cited above, as well as Lund and Delves (1998), Reviews of Reproduction 3:71-76, which states that:

[t]he glycoprotein hormones are 'self' antigens. Although normally expressed only during pregnancy, it appears that hCG is very effective at establishing immunological tolerance. There are hardly any reports of circulating autoantibodies to the hormone being detected in humans, even in patients with a history of recurrent spontaneous abortion (Tulppala *et al.*, 1992). However, it is also clear that this tolerance is not absolute, because when it is administered coupled to a potent carrier and in the presence of adjuvant, hCG can break tolerance and elicit an immune response.

(paragraph spanning pages 74-75) enclosed as Appendix A. Further evidence that the prior art believed the only relevant form of  $\beta$ hCG vaccine was one which was linked to an immunogen carrier, is provided by Triozzi *et al.* This reference describes conjugates of  $\beta$ hCG-CT coupled to diphtheria toxoid and combined with the adjuvant, muramyl dipeptide and a vehicle, squalene/mannide monooleate (Ann NY Acad Sci (1993); enclosed as Appendix B).

In contrast, Applicants developed an effective method for generating an immune response against  $\beta$ hCG, which does not require (but can include) foreign (non-self) T cell epitopes and adjuvants, as taught by the prior art. Moreover, Applicants were the first to show

that by linking  $\beta$ hCG to an anti-MMR-antibody, the presently claimed methods were capable of inducing a cytotoxic T cell response mediated by both CD4<sup>+</sup> and CD8<sup>+</sup> T cells against  $\beta$ hCG. Specifically,  $\beta$ hCG is targeted to the MMR and processed through both MHC class I and class II pathways. Thus, antigen-specific CTLs (*e.g.*, CD8<sup>+</sup> T cells) are activated, as well as other important effector T cells, including helper T cells (*e.g.*, CD4<sup>+</sup> T cells).

Based on at least the foregoing, the presently claimed methods are patentable.

***Rejection of Claims 41-43 Under 35 U.S.C. § 112, First Paragraph***

Claims 41-43 are rejected under 35 U.S.C. § 112, first paragraph, because according to the Examiner, while the specification is enabling for an antibody comprising a full complement of CDRs (*i.e.*, all six CDRs identified as SEQ ID NOs: 13-18), “does not reasonably provide enablement for any antibody comprising one specifically identified CDR from the VL and one specifically identified CDR from the VH chain as recited in claims 41-43.”

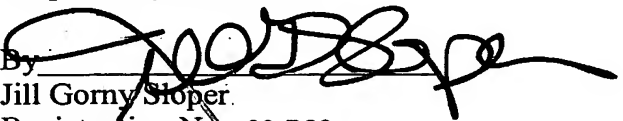
Applicants respectfully traverse this rejection. However, to expedite prosecution, claim 41 has been amended to specify a full complement of CDRs and claims 42 and 43 have been canceled.

**CONCLUSION**

Based on the foregoing amendments and arguments, reconsideration and withdrawal of all the rejections and allowance of this application with all pending claims are respectfully requested. If a telephone conversation with Applicants' Attorney would expedite the prosecution of the above-identified application, the Examiner is urged to call the undersigned at (617) 227-7400.

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Respectfully submitted,

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